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(54) Title: BICYCLIC HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF IMPOTENCE

(57) Abstract

The use of certain 5-arylpyrazolo[4,3-d]pyrimidin-7-ones, 6-arylpyrazolo[3,4-d]pyrimidin-4-ones, 2-arylquinazolin-4-ones, 2-arylpurin-6-ones and 2-arylpyrido[3,2-d]pyrimidin-4-ones, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man; a pharmaceutical composition for said treatment; and a method of said treatment of said animal with said pharmaceutical composition or with said either entity.

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BICYCLIC HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF IMPOTENCE

This invention relates to the use of certain pyrazolo[4,3-d]pyrimidin-7-ones, pyrazolo[3,4-d]pyrimidin-4-ones, quinazolin-4-ones, purin-6-ones and pyrido[3,2-d]pyrimidin-4-ones for the treatment of impotence.

Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

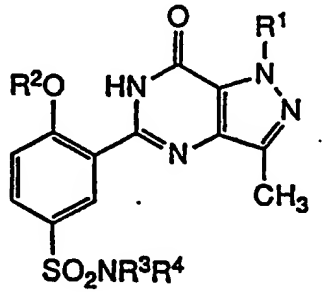
Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative

to the i.c. r ut is the use of glyceryl trinitrate (GTN) patches applied to the p nis, which has been shown to be effective but produc s side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in WO-A-93/06104, WO-A-93/07149, WO-A-93/12095, WO-A-94/00453 and WO-A-94/05661 respectively, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascul-r disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

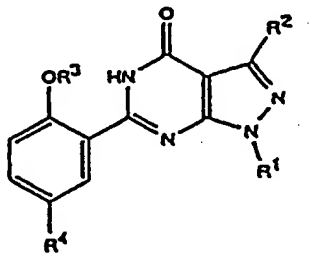
Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):



(I)

wherein R^1 is methyl or ethyl;
R^2 is ethyl or n-propyl;
and R^3 and R^4 are each independently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino;

a compound of formula (II):



(II)

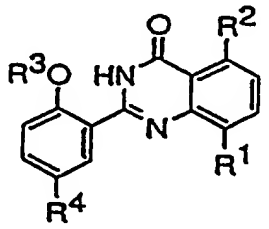
wherein R^1 is C_1-C_6 alkyl;
R^2 is H; methyl or ethyl;
R^3 is C_2-C_4 alkyl;
R^4 is H; C_1-C_4 alkyl optionally substituted with NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7 or halo;
R^5 and R^6 are each independently H or C_1-C_4

alkyl; or, together with the nitrogen atom to which they ar attached, form a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-pip razinyl or 1-imidazolyl group wherein said group is optionally substituted with one or two C_1-C_4 alkyl groups;

R^7 is H or C_1-C_4 alkyl;

and R^8 is H; C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

a compound of formula (III):



(III)

wherein R^1 is H; C_1-C_4 alkyl; C_1-C_4 alkoxy or $CONR^5R^6$;

R^2 is H or C_1-C_4 alkyl;

R^3 is C_2-C_4 alkyl;

R^4 is H; C_2-C_4 alkanoyl optionally substituted with NR^7R^8; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^7R^8; $CH=CHCO_2R^9$; $CH=CHCONR^7R^8$; $CH_2CH_2CO_2R^9$; $CH_2CH_2CONR^7R^8$; $SO_2NR^7R^8$; $SO_2NH(CH_2)_nNR^7R^8$ or imidazolyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl;

R^7 and R^8 are each independently H or C_1-C_4 alkyl; or, together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino or 4-(NR^{10})-1-piperazinyl group wherein any

of said groups is optionally substituted with $CONR^5R^6$;

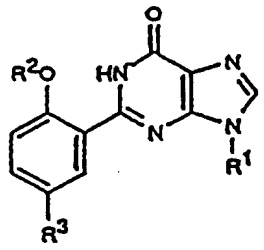
R^9 is H r C_1-C_4 alkyl;

R^{10} is H; C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

and n is 2, 3 or 4;

with the proviso that R^4 is not H when R^1 is H, C_1-C_4 alkyl or C_1-C_4 alkoxy;

a compound of formula (IV):



(IV)

wherein R^1 is C_1-C_4 alkyl;

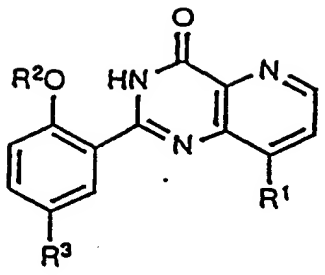
R^2 is C_2-C_4 alkyl;

R^3 is H or $SO_2NR^4R^5$;

R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-(NR^6)-1-piperazinyl group;

and R^6 is H or C_1-C_3 alkyl;

or a compound of formula (V):



(V)

wherein R^1 is H; C_1-C_4 alkyl; CN or $CONR^4R^5$;
R^2 is C_2-C_4 alkyl;
R^3 is $SO_2NR^6R^7$; NO_2; NH_2; $NHCOR^8$; $NHSO_2R^8$ or $N(SO_2R^8)_2$;
R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl;
R^6 and R^7 are each independently selected from H and C_1-C_4 alkyl optionally substituted with CO_2R^9, OH, pyridyl, 5-isoxazolin-3-onyl, morpholino or 1-imidazolidin-2-onyl; or, together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino, 1-pyrazolyl or 4-(NR^{10})-1-piperazinyl group wherein any of said groups may optionally be substituted with one or two substituents selected from C_1-C_4 alkyl, CO_2R^9, NH_2 and OH;
R^8 is C_1-C_4 alkyl or pyridyl;
R^9 is H or C_1-C_4 alkyl;
and R^{10} is H; C_1-C_4 alkyl or (hydroxy)C_2-C_3 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a

male animal, including man.

In the above definition, unless otherwise indicated, alkyl and alkoxy groups having three or more carbon atoms, and alkenyl and alkanoyl groups having four carbon atoms, may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of the invention may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore, certain compounds of formulae (II) and (III) which contain alkenyl groups may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the invention may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of the invention which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. The compounds of the invention can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts. For a review on suitable pharmaceutical salts, see J. Pharm. Sci., 1977, 66, 1.

A preferred group of compounds is that of formula (I) wherein R^3 is H; methyl or ethyl; R^4 is C_1-C_6 alkyl optionally substituted with cyclohexyl or with morpholino; and R^1 and R^2 are as previously defined for formula (I); of formula (II) wherein R^1 is n-propyl; R^2 is H or methyl; R^3 is ethyl or n-propyl; R^4 is H; ethyl substituted with $CONR^5R^6$ or CO_2R^7; vinyl substituted with $CONR^5R^6$ or CO_2R^7; acetyl substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7 or bromo; R^5 and R^6

together with the nitrogen atom to which they are attached form a morpholino, 4-(NR^8)-1-piperazinyl or 2,4-dimethyl-1-imidazolyl group; R^7 is H or t-butyl; and R^8 is methyl or 2-hydroxyethyl; of formula (III) wherein R^1 is H; methyl; methoxy or $CONR^5R^6$; R^2 is H or methyl; R^3 is ethyl or n-propyl; R^4 is H; acetyl optionally substituted with NR^7R^8; hydroxyethyl substituted with NR^7R^8; $CH=CHCO_2R^9$; $CH=CHCONR^7R^8$; $CH_2CH_2CO_2R^9$; $SO_2NR^7R^8$; $SO_2NH(CH_2)_3NR^7R^8$ or 1-imidazolyl; R^5 and R^6 are each independently H or ethyl; R^7 and R^8 together with the nitrogen atom to which they are attached form a piperidino, 4-carbamoylpiperidino, morpholino or 4-(NR^{10})-1-piperazinyl group; R^9 is H or t-butyl; and R^{10} is H; methyl or 2-hydroxyethyl; with the proviso that R^4 is not H when R^1 is H, methyl or methoxy; of formula (IV) wherein R^1 and R^2 are each independently ethyl or n-propyl; R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-(NR^6)-1-piperazinyl group; and R^3 and R^6 are as previously defined for formula (IV); and of formula (V) wherein R^1 is H; n-propyl; CN or $CONH_2$; R^2 is ethyl; R^3 is $SO_2NR^6R^7$; NO_2; NH_2; $NHCOCH(CH_3)_2$; $NHSO_2CH(CH_3)_2$; $NHSO_2$(3-pyridyl) or $N[SO_2(3\text{-pyridyl})]_2$; R^6 is H; methyl or 2-hydroxyethyl; R^7 is methyl optionally substituted with 2-pyridyl or 5-isoxazolin-3-onyl; or ethyl 2-substituted with OH, $CO_2CH_2CH_3$, morpholino or 1-imidazolidin-2-onyl; or R^6 and R^7 together with the nitrogen atom to which they are attached form a (4-CO_2R^9)piperidino, 5-amino-3-hydroxy-1-pyrazolyl or 4-(NR^{10})-1-piperazinyl group; R^9 is H or ethyl; and R^{10} is H; methyl or 2-hydroxyethyl.

A particularly preferred group of compounds is that of formula (III) wherein R^1 is methyl; $CONH_2$ or $CONHCH_2CH_3$; R^2 is H; R^3 is ethyl or n-propyl; R^4 is H; acetyl; 1-hydroxy-2-(NR^7R^8)ethyl; $CH=CHCO_2C(CH_3)_3$; $CH=CHCONR^7R^8$; $SO_2NR^7R^8$ or 1-imidazolyl; R^7 and R^8

together with the nitrogen atom to which they are attach d form a 4-(NR^{10})-1-piperazinyl group; and R^{10} is methyl or 2-hydroxyethyl; with the proviso that R^4 is not H when R^1 is methyl; of formula (IV) wherein R^1 is n-propyl; R^2 is ethyl; and R^3 is 1-piperazinylsulphonyl or 4-methyl-1-piperazinylsulphonyl; and of formula (V) wherein R^1 is n-propyl or CN; R^2 is ethyl; R^3 is $SO_2NR^6R^7$; $NHSO_2CH(CH_3)_2$; $NHSO_2$(3-pyridyl) or $N[SO_2(3\text{-pyridyl})]_2$; R^6 is H or methyl; R^7 is methyl; or ethyl 2-substituted with $CO_2CH_2CH_3$; morpholino or 1-imidazolidin-2-onyl; or R^6 and R^7 together with the nitrogen atom to which they are attached form a (4-CO_2R^9)piperidino or 4-(NR^{10})-1-piperazinyl group; R^9 is H or ethyl; and R^{10} is H; methyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxyphenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxyphenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one;

2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one;

8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one;

8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one;

2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;

2-[5-(4-carboxypiperidinosulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;

and 2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one.

The compounds of formulae (I), (II), (III), (IV) and (V) and their pharmaceutically acceptable salts, processes for the preparation thereof, in vitro test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, pharmaceutical compositions thereof and routes of administration for human use, are described in WO-A-93/06104, WO-A-93/07149, WO-A-93/12095, WO-A-94/00453 and WO-A-94/05661 respectively, which are incorporated herein by

reference.

A preliminary investigation was carried out with a view to isolating and characterising the cyclic nucleotide PDEs of human corpus cavernosum, relaxation of which leads to penile erection. Studies of substrate specificity, response to activators and inhibitor sensitivity, have demonstrated that human corpus cavernosum contains three distinct PDE enzymes.

Methods

Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2-4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250mM sucrose, 1mM EDTA, 0.5mM PMSF and 20mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with teflon pestles and soluble fraction was prepared by centrifugation at 100,000 x g for 60 min. at 4°C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1mM EDTA, 0.5 mM PMSF and 20mM HEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0-500mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500nM cGMP or 500nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1μM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10mM $CaCl_2$ and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4°C during the

c urse of the study.

Inhibition studies were performed using a substrate concentration of 500nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3 x 10^{-10} to 1 x 10^{-4}M in half log increments. IC_{50} values were calculated using the sigmoidal curve fitting algorithm of biostat.

Results

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represents the major PDE present and is highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE_V. Fraction II hydrolyses cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and is classified as PDE_{II}, whilst fraction III is cAMP selective and this activity is inhibited in the presence of cGMP, consistent with PDE_{III} activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE_V, whilst fraction III was clearly identified as PDE_{III}; fraction II (PDE_{II}) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE is the cGMP-specific PDE_V, whilst cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III}

are also pr sent.

Certain compounds of the invention have been tested in vitro and found to be potent and selective inhibitors of the cGMP-specific PDE_V. Thus relaxation of the corpus cavernosum tissue and consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances, and of premature labour and dysmenorrhea.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of the invention or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt

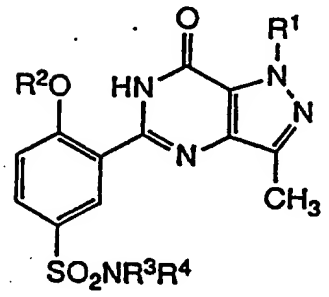
thereof, togeth r with a pharmaceutically acceptable diluent or carrier.

Ther is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), (II), (III), (IV) or (V), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

CLAIMS

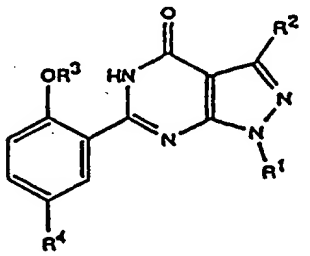
1. The use of a compound of formula (I):



(I)

wherein R^1 is methyl or ethyl;
R^2 is ethyl or n-propyl;
and R^3 and R^4 are each independently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino;

a compound of formula (II):

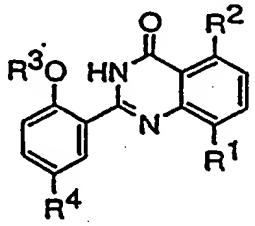


(II)

wherein R^1 is C_1-C_6 alkyl;
R^2 is H; methyl or ethyl;
R^3 is C_2-C_4 alkyl;
R^4 is H; C_1-C_4 alkyl optionally substituted with NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl

opti nally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7 or halo;
R^5 and R^6 are each independently H or C_1-C_4 alkyl; or, together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted with one or two C_1-C_4 alkyl groups;
R^7 is H or C_1-C_4 alkyl;
and R^8 is H; C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

a compound of formula (III):



(III)

wherein R^1 is H; C_1-C_4 alkyl; C_1-C_4 alkoxy or $CONR^5R^6$;
R^2 is H or C_1-C_4 alkyl;
R^3 is C_2-C_4 alkyl;
R^4 is H; C_2-C_4 alkanoyl optionally substituted with NR^7R^8; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^7R^8; $CH=CHCO_2R^9$; $CH=CHCONR^7R^8$; $CH_2CH_2CO_2R^9$; $CH_2CH_2CONR^7R^8$; $SO_2NR^7R^8$; $SO_2NH(CH_2)_nNR^7R^8$ or imidazolyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl;
R^7 and R^8 are each independently H or C_1-C_4

alkyl; or, together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino or 4-(NR^{10})-1-piperazinyl group wherein any of said groups is optionally substituted with $CONR^5R^6$;

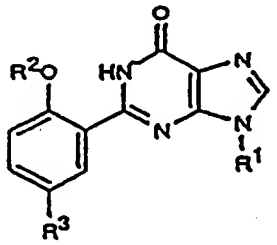
R^9 is H or C_1-C_4 alkyl;

R^{10} is H; C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

and n is 2, 3 or 4;

with the proviso that R^4 is not H when R^1 is H, C_1-C_4 alkyl or C_1-C_4 alkoxy;

a compound of formula (IV):



(IV)

wherein R^1 is C_1-C_4 alkyl;

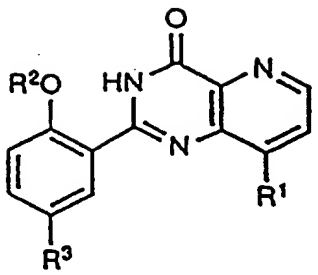
R^2 is C_2-C_4 alkyl;

R^3 is H or $SO_2NR^4R^5$;

R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-(NR^6)-1-piperazinyl group;

and R^6 is H or C_1-C_3 alkyl;

or a compound of formula (V):



(V)

wherein R^1 is H; C_1-C_4 alkyl; CN or $CONR^4R^5$;
R^2 is C_2-C_4 alkyl;
R^3 is $SO_2NR^6R^7$; NO_2; NH_2; $NHCOR^8$; $NHSO_2R^8$ or $N(SO_2R^8)_2$;
R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl;
R^6 and R^7 are each independently selected from H and C_1-C_4 alkyl optionally substituted with CO_2R^9, OH, pyridyl, 5-isoxazolin-3-onyl, morpholino or 1-imidazolidin-2-onyl; or, together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino, 1-pyrazolyl or 4-(NR^{10})-1-piperazinyl group wherein any of said groups may optionally be substituted with one or two substituents selected from C_1-C_4 alkyl, CO_2R^9, NH_2 and OH;
R^8 is C_1-C_4 alkyl or pyridyl;
R^9 is H or C_1-C_4 alkyl;
and R^{10} is H; C_1-C_4 alkyl or (hydroxy)C_2-C_3 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

2. The use according to claim 1 wherein in a compound of formula (I) R^3 is H; methyl or ethyl; R^4 is C_1-C_6 alkyl optionally substituted with cyclohexyl or with morpholino; and R^1 and R^2 are as previously defined in claim 1; in a compound of formula (II) R^1 is n-propyl; R^2 is H or methyl; R^3 is ethyl or n-propyl; R^4 is H; ethyl substituted with $CONR^5R^6$ or CO_2R^7; vinyl substituted with $CONR^5R^6$ or CO_2R^7; acetyl substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7 or bromo; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino, 4-(NR^8)-1-piperazinyl or 2,4-dimethyl-1-imidazolyl group; R^7 is H or t-butyl; and R^8 is methyl or 2-hydroxyethyl; in a compound of formula (III) R^1 is H; methyl; methoxy or $CONR^5R^6$; R^2 is H or methyl; R^3 is ethyl or n-propyl; R^4 is H; acetyl optionally substituted with NR^7R^8; hydroxyethyl substituted with NR^7R^8; $CH=CHCO_2R^9$; $CH=CHCONR^7R^8$; $CH_2CH_2CO_2R^9$; $SO_2NR^7R^8$; $SO_2NH(CH_2)_3NR^7R^8$ or 1-imidazolyl; R^5 and R^6 are each independently H or ethyl; R^7 and R^8 together with the nitrogen atom to which they are attached form a piperidino, 4-carbamoylpiperidino, morpholino or 4-(NR^{10})-1-piperazinyl group; R^9 is H or t-butyl; and R^{10} is H; methyl or 2-hydroxyethyl; with the proviso that R^4 is not H when R^1 is H, methyl or methoxy; in a compound of formula (IV) R^1 and R^2 are each independently ethyl or n-propyl; R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-(NR^6)-1-piperazinyl group; and R^3 and R^6 are as previously defined in claim 1; and in a compound of formula (V) R^1 is H; n-propyl; CN or $CONH_2$; R^2 is ethyl; R^3 is $SO_2NR^6R^7$; NO_2; NH_2; $NHCOCH(CH_3)_2$;

$NHSO_2CH(CH_3)_2$; $NHSO_2$(3-pyridyl) or $N[SO_2(3\text{-pyridyl})]_2$; R^6 is H; methyl or 2-hydroxyethyl; R^7 is methyl optionally substituted with 2-pyridyl or 5-isoxazolin-3-onyl; or ethyl 2-substituted with OH, $CO_2CH_2CH_3$, morpholino or 1-imidazolidin-2-onyl; or R^6 and R^7 together with the nitrogen atom to which they are attached form a (4-CO_2R^9)piperidino, 5-amino-3-hydroxy-1-pyrazolyl or 4-(NR^{10})-1-piperazinyl group; R^9 is H or ethyl; and R^{10} is H; methyl or 2-hydroxyethyl.

3. The use according to claim 2 wherein in a compound of formula (III) R^1 is methyl; $CONH_2$ or $CONHCH_2CH_3$; R^2 is H; R^3 is ethyl or n-propyl; R^4 is H; acetyl; 1-hydroxy-2-(NR^7R^8)ethyl; $CH{=}CHCO_2C(CH_3)_3$; $CH{=}CHCONR^7R^8$; $SO_2NR^7R^8$ or 1-imidazolyl; R^7 and R^8 together with the nitrogen atom to which they are attached form a 4-(NR^{10})-1-piperazinyl group; and R^{10} is methyl or 2-hydroxyethyl; with the proviso that R^4 is not H when R^1 is methyl; in a compound of formula (IV) R^1 is n-propyl; R^2 is ethyl; and R^3 is 1-piperazinylsulphonyl or 4-methyl-1-piperazinylsulphonyl; and in a compound of formula (V) R^1 is n-propyl or CN; R^2 is ethyl; R^3 is $SO_2NR^6R^7$; $NHSO_2CH(CH_3)_2$; $NHSO_2$(3-pyridyl) or $N[SO_2(3\text{-pyridyl})]_2$; R^6 is H or methyl; R^7 is methyl; or ethyl 2-substituted with $CO_2CH_2CH_3$; morpholino or 1-imidazolidin-2-onyl; or R^6 and R^7 together with the nitrogen atom to which they are attached form a (4-CO_2R^9)piperidino or 4-(NR^{10})-1-piperazinyl group; R^9 is H or ethyl; and R^{10} is H; methyl or 2-hydroxyethyl.

4. The use according to claim 2 or claim 3 wherein the compound of formula (I), (II), (III), (IV) or (V) is selected from

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxyphenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxyphenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-

pyrimidin-7-one;

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyph nyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one;

2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one;

8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one;

8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one;

2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;

2-[5-(4-carboxypiperidinosulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;

2-{2-ethoxy-5-[4-(2-hydroxy thyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;
and 2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one.

5. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), (II), (III), (IV) or (V) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

6. A method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), (II), (III), (IV) or (V) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

7. The use of a compound of formula (I), (II), (III), (IV) or (V) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction, premature labour or dysmenorrhea.

8. A method of treating a female animal, including woman, to cure or prevent sexual dysfunction, premature labour or dysmenorrhea which comprises treating said female animal with an effective amount of a compound of formula (I), (II), (III), (IV) or (V) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 95/04065

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,94 28902 (PFIZER LTD) 22 December 1994 see claims	1-6
Y	WO,A,94 00453 (PFIZER LTD) 6 January 1994 cited in the application see claims 1-7	1-6
Y	WO,A,93 06104 (PFIZER LTD) 1 April 1993 cited in the application see claims 1-7	1-6
Y	WO,A,93 12095 (PFIZER LTD) 24 June 1993 cited in the application see claims 1-8	1-6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
24 January 1996	07.02.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 07149 (PFIZER LTD) 15 April 1993 cited in the application see claims 1-7	1-6
Y	WO,A,94 05661 (PFIZER LTD) 17 March 1994 cited in the application see claims 1-7	1-6
Y	AM. J. PHYSIOL. HEART CIRC. PHYSIOL., vol. 264, no. 2, 1993 pages h419-h422, F. TRIGA-ROCHA ET AL 'Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs.' see the whole document	1-6
A	NEUROL URODYN., vol. 13, no. 1, 1994 pages 71-80, F. TRIGO-ROCHA ET AL. 'Intracellular mechanism of penile erection in monkeys.'	
A	EP,A,0 535 924 (MERCK FROSST CANADA INC) 7 April 1993	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/04065

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9428902	22-12-94	AU-B-	6797394	03-01-95
		NO-A-	954757	24-11-95
WO-A-9400453	06-01-94	CA-A-	2139109	06-01-94
		EP-A-	0647227	12-04-95
		FI-A-	946083	23-12-94
		JP-T-	7504681	25-05-95
WO-A-9306104	01-04-93	PT-A-	100862	30-11-93
WO-A-9312095	24-06-93	CA-A-	2122360	24-06-93
		EP-A-	0628032	14-12-94
		FI-A-	942769	10-06-94
		JP-T-	7502029	02-03-95
		US-A-	5482941	09-01-96
WO-A-9307149	15-04-93	PT-A-	100915	29-10-93
WO-A-9405661	17-03-94	CA-A-	2138298	17-03-94
		EP-A-	0656898	14-06-95
		FI-A-	950889	27-02-95
		JP-T-	7506838	27-07-95
EP-A-535924	07-04-93	JP-A-	7215934	15-08-95
		US-A-	5273980	28-12-93

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/04065

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6+8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published
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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: cGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

(57) Abstract

Compounds which are selective inhibitors of cGMP PDE are useful in the treatment of erectile dysfunction (impotence) in male animals, including man.

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cGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

This invention relates to the use of compounds which are selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in the treatment of erectile dysfunction (impotence) in male animals, including man.

Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term

success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

According to the specification of our International patent application no PCT/EP94/01580, (publication no WO94/28902), we describe and claim the use of a series of pyrazolo [4,3-d]pyrimidin-7-ones for the treatment of impotence. The compounds are potent and selective inhibitors of cGMP PDE in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities previously disclosed for the compounds in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome. The specification goes on to describe investigations which identified three PDE isoenzymes in human corpus cavenosum tissue, relaxation of which leads to penile erection. The predominant enzyme was found to be the cGMP-specific PDE_V, while cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III}, were also present. The compounds described were found to be potent and selective inhibitors of the PDE_V enzyme but demonstrated only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes. This activity is believed to be responsible for the action of the compounds in the treatment of erectile dysfunction.

A number of cGMP-PDE inhibitors have previously been described in the literature for a variety of utilities, these include use in treating obstructive lung diseases such as asthma and brochitis, in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria, and irritable bowel syndrome; and in combatting angina, hypertension and congestive heart failure. Utility has also been claimed as diuretics, as antiinflammatory agents, in the treatment of baldness, for conditions of reduced blood vessel patency, and in glaucoma. However there has not previously been any suggestion that any of these compounds would be of utility in the treatment of erectile dysfunction.

Thus the present invention provid s the use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

i a 5-substituted pyrazolo [4,3-d]pyrimidine-7-one as disclosed in European patent application 0201188;

ii a griseolic acid derivative as disclosed in European patent applications nos 0214708 and 0319050;

iii a 2-phenylpurinone derivative as disclosed in European patent application 0293063;

iv a phenylpyridone derivative as disclosed in European patent application 0347027;

v a fused pyrimidine derivative as disclosed in European patent application 0347146;

vi a condensed pyrimidine derivative as disclosed in European patent application 0349239;

vii a pyrimidopyrimidine derivative as disclosed in European patent application 0351058;

viii a purine compound as disclosed in European patent application 0352960;

ix a quinazolinone derivative as disclosed in European patent application 0371731;

x a phenylpyrimidone derivative as disclosed in European patent application 0395328;

xi an imidazoquinoxalinone derivative or its aza analogue as disclosed in European patent application 0400583;

xii a phenylpyrimidone derivative as disclosed in European patent application 0400799;

xiii a phenylpyridone derivative as disclosed in European patent application 0428268;

xiv a pyrimidopyrimidine derivative as disclosed in European patent 0442204;

xv a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

xvi a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in European patent application 0584487;

xvii a polycyclic guanine derivative as disclosed in International patent application WO91/19717;

xviii a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

xix a 2-benzyl-polycyclic guanine derivative as disclosed in International patent application WO 94/19351;

xx a quinazoline derivative as disclosed in US patent 4060615;

xxi a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US patent 5294612;

xxii a benzimidazole as disclosed in Japanese patent application 5-222000; or

xxiii a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.

xxiv a N-containing heterocycle as disclosed in International patent application WO94/22855.

The invention includes the use of any compound within the scope of the claims of the patents listed above as well as the particular individual compounds disclosed therein.

Of particular interest for use in the present invention are compounds disclosed in EP 0579496, WO93/07124, US 5294612 and WO94/22855 (xv, xviii, xxi and xxiv above); the compounds of EP 0579496 and WO94/22855 being especially preferred.

Examples of particular and preferred compounds from these patents and publications for use in the present invention include:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one (preparation as described in European patent application 201188, Example 1),

2-(2-propoxyphenyl)-6-purinone (preparation as described in European patent application 0293063, Example 1),

6-(2-propoxyphenyl)-l,2-dihydro-2-oxopyridine-3-carboxamide (preparation as described in European patent application 0347027, Example 2),

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one (preparation as described in European pat nt application 0347146, Example 1),

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (preparation as described in European patent application 0351058, Example 1),

6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide (preparation as described in European patent application 0395328, Example 15),

1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one (preparation as described in European patent application 0400583),

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline (preparation as described in European patent application 0579496, Example 5(c)),

5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine (preparation as described in European patent application 0584487, Example 1),

5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one (preparation as described in International patent application WO 91/19717, Example 9A3),

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124),

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one(preparation as described in International Patent application WO94/19351, Example 14),

1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90),

1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one, (preparation as described in US patent 5294612, Example 83),

2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole (preparation described in Japanese patent application 5-222000),

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (pr paration described in International patent application WO94/22855, Example II),

and 2-phenyl-8-ethoxycycloheptimidazole (KT2-734).

Of particular interest f r use in the present invention are the compounds: 4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline (preparation as described in European patent application 0579496, Example 5(c)), 1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124), (6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one(preparation as described in International Patent application WO94/19351, Example 14), 1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90), 1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one, as described in US patent 5294612, Example 83), or 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (preparation described in International patent application WO94/22855, Example II),

Further cGMP PDE inhibitors for use in the treatment of erectile dysfunction are:

xxv a pyrazolopyrimidine derivative as disclosed in European patent application 0636626;

xxvi a 4-aminopyrimidine derivative as disclosed in European patent application 0640599;

xxvii a imidazoquinazoline derivative as disclosed in International patent application WO95/06648;

xxviii an anthranilic acid derivative as disclosed in International patent application WO95/18097;

xxix a 4-aminoquinazoline derivative as disclosed in US patent 5436233;

xxx a tetracyclic derivative as disclosed in International patent application WO95/19978;

xxxi a imidazoquinazoline derivative as disclosed in European pat nt application 0668280; or

xxxii a quinazoline compound as disclosed in European patent application 0669324.

Th compounds may be evaluated as s lectiv inhibitors of cGMP-PDE using any of the methods previously described but in particular their activity against cGMP-PDE$_v$ may be assessed as described in our International patent application PCT/EP94/01580, (WO94/28902).

Generally, in man, oral administration is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound daily, however the dosage may be increased depending on the potency of the compound being administered and higher dosages are within the scope of the invention. Alternative dosage regimes are also possible depending upon the individual patients circumstances such as the frequency of sexual intercourse. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of the invention or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they are also useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances, premature labour and dysmenorrhea.

The invention also provides a method of treating erectile dysfunction in a male animal which comprises administering an effective amount of a compound which is a selective cGMP-PDE inhibitor as defined above.

CLAIMS

1. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

i a 5-substituted pyrazolo [4,3-d]pyrimdine-7-one as disclosed in European patent application 0201188;

ii a griseolic acid derivative as disclosed in European patent applications nos 0214708 and 0319050;

iii a 2-phenylpurinone derivative as disclosed in European patent application 0293063;

iv a phenylpyridone derivative as disclosed in European patent application 0347027;

v a fused pyrimidine derivative as disclosed in European patent application 0347146;

vi a condensed pyrimidine derivative as disclosed in European patent application 0349239;

vii a pyrimidopyrimidine derivative as disclosed in European patent application 0351058;

viii a purine compound as disclosed in European patent application 0352960;

ix a quinazolinone derivative as disclosed in European patent application 0371731;

x a phenylpyrimidone derivative as disclosed in European patent application 0395328;

xi an imidazoquinoxalinone derivative or its aza analogue as disclosed in European patent application 0400583;

xii a phenylpyrimidone derivative as disclosed in European patent application 0400799;

xiii a phenylpyridone derivative as disclosed in European patent application 0428268;

xiv a pyrimidopyrimidine derivative as disclos d in European patent 0442204;

xv a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

xvi a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in European patent application 0584487;

xvii a polycyclic guanine derivative as disclosed in International patent application WO91/19717;

xviii a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

xix a 2-benzyl-polycyclic guanine derivative as disclosed in International patent application WO 94/19351;

xx a quinazoline derivative as disclosed in US patent 4060615

xxi a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US patent 5294612

xxii a benzimidazole as disclosed in Japanese patent application 5-222000; or

xxiii a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.

xxiv a N-containing heterocycle as disclosed in International patent application WO94/22855.

2. The use of a compound as claimed in claim 1 wherein said compound is:

a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

a 6-heterocyclyl pyrazolo [3,4-d]pyrimid-4-one as disclosed in US patent 5294612 or

a N-containing heterocycle as disclosed in International patent application WO94/22855.

3. The use of a compound as claimed in claim 1 wherein said compound is:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one;

2-(2-propoxyphenyl)-6-purinone;

6-(2-propoxyphenyl)-l,2-dihydro-2-oxopyridine-3-carboxamide;

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-on ;
7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine;
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide;
1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one;
4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;
5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine;
5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one
1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;
2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole;
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;
or 2-phenyl-8-ethoxycycloheptimidazole.

4. The use of a compound as claimed in claim 3 where said compound is:
4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;
1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;
or
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;

5. The use of a compound which is a selectiv cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

xxv a pyrazolopyrimidine derivative as disclosed in European patent application 0636626;

xxvi a 4-aminopyrimidine derivative as disclosed in European patent application 0640599;

xxvii a imidazoquinazoline derivative as disclosed in International patent application WO95/06648;

xxviii an anthranilic acid derivative as disclosed in International patent application WO95/18097;

xxix a 4-aminoquinazoline derivative as disclosed in US patent 5436233;

xxx a tetracyclic derivative as disclosed in International patent application WO95/19978;

xxxi a imidazoquinazoline derivative as disclosed in European patent application 0668280; or

xxxii a quinazoline compound as disclosed in European patent application 0669324.

6. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction, premature labour or dysmenorrhea, wherein said compound is a compound as previously claimed in any one of claims 1 to 5 for use in the treatment of erectile dysfunction in a male.

7. A method for the treatment of erectile dysfunction in a male animal or female sexual dysfunction, premature labour or dysmenorrhea, which comprises administering an effective amount of a compound which is a selective cGMP PDE inhibitor as previously claimed in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/EP 95/04066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AM.J.PHYSIOL., vol. 264, no. 2, 1993, pages 419-22, XP002000726 "Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs" see abstract see page 420, right-hand column, line 20 - line 24 see page 422, left-hand column, last paragraph ---	1-7
Y	EP,A,0 442 204 (SMITHKLINE BEECHAM) 21 August 1991 cited in the application see page 3, paragraph 1 ---	1-7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1996	09 May 1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gerli, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/EP 95/04066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 293 063 (SMITH KLINE & FRENCH LAB.) 30 November 1988 cited in the application see page 2, paragraph 1	1-7
Y	EP,A,0 371 731 (SMITHKLINE BEECHAM) 6 June 1990 cited in the application see page 2, paragraph 1	1-7
Y,P	WO,A,94 29277 (SMITHKLINE BEECHAM) 22 December 1994 see page 1, paragraph 1	1-7
Y,P	ABSTRACTS OF PAPERS AMERICAN CHEMICAL SOCIETY, vol. 210, no. 1-2, 1995, page MEDI 229. XP002000727 "uk-92480 a potent and selective inhibitor of type va cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction" abstract no. 229	1-7

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/04066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 7 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/EP 95/04066

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-442204	21-08-91	JP-A-	3261785	21-11-91
EP-A-293063	30-11-88	AU-B-	599452	19-07-90
		AU-B-	1095688	04-08-88
		CA-A-	1303037	09-06-92
		DE-A-	3869205	23-04-92
		JP-A-	63196585	15-08-88
		US-A-	4885301	05-12-89
		ZA-A-	8800680	03-08-88
EP-A-371731	06-06-90	AU-B-	630638	05-11-92
		AU-B-	4541689	07-06-90
		CA-A-	2003690	31-05-90
		DE-D-	68914793	26-05-94
		DE-T-	68914793	18-08-94
		JP-A-	2193983	31-07-90
		PT-B-	92437	09-08-95
		US-A-	5147875	15-09-92
WO-A-9429277	22-12-94	NONE		